10676089

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(FILE 'HOME' ENTERED AT 19:03:41 ON 07 JUL 2005)

FILE 'MEDLINE' ENTERED AT 19:03:48 ON 07 JUL 2005

L1	126953	S	CYTOKINE?
L2	883	S	IL1
L3	51057	S	TNF
L4	343	S	L2 AND L3
L5	4	S	L4 AND REVIEW
L6	256	S	L1 AND L4
L7	4	S	L6 AND REVIEW
L8	0	S	L7 NOT L5
L9	4	S	L6 AND REVIEW
L10	6290	S	L1 AND REVIEW
L11	42	S	INTERLUKIN
L12	139287	S	INTERLEUKIN?
L13	66802	S	TUMOR NECROSIS FACTOR
L14	30312	S	L12 AND L13
L15	21791	S	L1 AND L14
L16	431	S	L15 AND REVIEW
L17	4	S	L16 AND SEPTICEMIA
L18	4466	S	L15 AND INFLAMMATION
L19	83	S	L18 AND PAIN
L20	10	S	L19 AND REVIEW
L21	10381	S	INFLAMMATORY CYTOKINE?
L22	654	S	L21 AND REVIEW?
L23	186	S	L22 AND INTERLEUKIN
L24	101	S	L23 AND TUMOR NECROSIS
L25	79	S	L24 AND REVIEW
L26	31	S	L25 AND INHIBIT?
L27	9	S	L26 AND PRODUCTION
L28	22	S	L26 NOT L27

FILE 'STNGUIDE' ENTERED AT 19:25:04 ON 07 JUL 2005

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10676089

=> d 1-9 bib abs

L27 ANSWER 1 OF 9 MEDLINE on STN
AN 2003447100 MEDLINE
DN PubMed ID: 14508150
TI Insulin: an endogenous cardioprotector.
AU Das Undurti N
CS EFA Sciences LLC, Norwood, Massachusetts 02062, USA.. Undurti@hotmail.com
SO Current opinion in critical care, (2003 Oct) 9 (5) 375-83. Ref: 75
Journal code: 9504454. ISSN: 1070-5295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200401
ED Entered STN: 20030926
Last Updated on STN: 20040123
Entered Medline: 20040122
AB This **review** discusses the myocardial protective property of the insulin/glucose-insulin-potassium regimen and the mechanisms involved in this beneficial action. Several recent studies suggest that insulin not only is useful to control hyperglycemia and maintain glucose homeostasis but also may have the unique property to protect the myocardium from reperfusion injury and ischemia and prevent apoptosis of myocardial cells. The insulin/glucose-insulin-potassium (GIK) regimen suppresses the **production** of **tumor necrosis** factor-alpha, **interleukin**-6, macrophage migration **inhibitory** factor and other pro-**inflammatory cytokines**, and free radicals; and enhances the synthesis of endothelial nitric oxide and anti-**inflammatory cytokines interleukin**-4 and **interleukin**-10. Thus, the insulin/GIK regimen brings about its cardioprotective action. This may also explain why the insulin/GIK regimen is useful in sepsis and septic shock, myocardial recovery in acute myocardial infarction, and critical illness. It is suggested that the infusion of adequate amounts of insulin to patients with acute myocardial infarction, congestive heart failure, cardiogenic shock, and critical illness preserves myocardial integrity and function and ensures rapid recovery. In view of the suppressive action of insulin on the synthesis of proinflammatory cytokines and free radicals, it is possible that the insulin/GIK regimen, when used in a timely and appropriate fashion, may also protect other tissues and organs and facilitate in the recovery of patients who are critically ill.

L27 ANSWER 2 OF 9 MEDLINE on STN
AN 2003374702 MEDLINE
DN PubMed ID: 12909295
TI Cerebral pattern of pro- and anti-**inflammatory cytokines** in dementias.
AU Tarkowski Elisabeth; Liljeroth Ann Marie; Minthon Lennart; Tarkowski Andrzej; Wallin Anders; Blennow Kaj
CS Department of Rheumatology, Section of Neurology and Neurochemistry, University of Goteborg, S-413 46 Goteborg, Sweden.. elisabeth.tarkowski@immuno.gu.se
SO Brain research bulletin, (2003 Aug 15) 61 (3) 255-60. Ref: 51
Journal code: 7605818. ISSN: 0361-9230.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200310
ED Entered STN: 20030812
Last Updated on STN: 20031015
Entered Medline: 20031014
AB The knowledge regarding putative inflammatory component(s) participating in Alzheimer's disease (AD) and vascular dementia (VAD) is scarce. Recently, we have demonstrated the presence of certain **inflammatory cytokines** in the cerebrospinal fluid (CSF) of demented patients. Although the initial event(s) triggering the neurodegenerative processes in AD versus VAD may be different and lead to different neuropathological changes, it may initiate a similar cascade of cytokine **production** in response to neuronal injury. The cytokines released in the central nervous system (CNS) may, in turn, act in a similar manner in both diseases, amplifying some pathological changes such as amyloidogenesis and white matter lesions or on the contrary acting as neuroprotective molecules. This **review** will focus on the intracerebral **production** of the pro- and anti-**inflammatory cytokines interleukin** IL-1beta, IL-1 receptor antagonist (IL-1ra), IL-6 and TNF-alpha in dementia, and their relation to gene polymorphism, to cerebral neuronal damage, apoptosis, and to clinical variables of dementia. Our results, which show for the first time strikingly increased CSF levels of TNF-alpha but not of TNF-beta, IL-1beta or IL-6 in AD and VAD, may form a conceptual framework for further studies of neuroprotective mechanisms in dementias.

L27 ANSWER 3 OF 9 MEDLINE on STN
AN 2003173193 MEDLINE
DN PubMed ID: 12690937
TI Systemic inflammatory response to exhaustive exercise. Cytokine kinetics.
AU Suzuki Katsuhiko; Nakaji Shigeyuki; Yamada Mutsuo; Totsuka Manabu; Sato Koki; Sugawara Kazuo
CS Department of Hygiene, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562, Japan.. katsu@cc.hirosaki-u.ac.jp
SO Exercise immunology review, (2002) 8 6-48. Ref: 177
Journal code: 9505535. ISSN: 1077-5552.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20030416
Last Updated on STN: 20030626
Entered Medline: 20030625
AB It has been documented that strenuous exercise not only induces pyrogenesis but also elicits mobilization and functional augmentation of neutrophils and monocytes whereas it suppresses cellular immunity leading to increased susceptibility to infections. As mediators of these phenomena, cytokines released into the circulation have been a recent focus of attention. Indeed, there are as many as one hundred original reports concerning exercise and cytokines, and half of them have been

published in rapid succession from 2000, resulting in a tremendous accumulation of new knowledge within such a short term. The first aim of this **review** is to comprehensively summarize previous studies on systemic cytokine kinetics following exercise, with a special focus on reproducibility and quantitative comparison in human studies using specific immunoassays. Although **tumor necrosis** factor (TNF)-alpha and **interleukin** (IL)-1 beta have traditionally been understood to be the main inducer cytokines of acute phase reactions, the majority of studies have shown that the circulating concentration of these cytokines is either unchanged following exercise, or exhibits relatively small, delayed increments. Plasma interferon (IFN)-alpha and IFN-gamma do not appear to change following exercise, whereas IL-2 decreases after endurance exercise. The small changes of these proinflammatory and immunomodulatory cytokines could well be mediated by anti-**inflammatory cytokines** such as IL-1 receptor antagonist (IL-1ra), IL-6 and IL-10 and cytokine **inhibitors** (cortisol, prostaglandin E2 and soluble receptors against TNF and IL-2), which are known to increase markedly in the circulation following endurance exercise. Moreover, it has been recently demonstrated that endurance exercise induces systemic release of granulocyte colony-stimulating factor (G-CSF), macrophage CSF (M-CSF), IL-8 and monocyte chemotactic protein 1 (MCP-1). Although the majority of available data have been obtained following prolonged exercise, it remains to be elucidated whether short-duration intensive exercise also causes rapid systemic cytokine release. In addition, there have been few studies that have simultaneously compared the extent of each cytokine response to exercise from a wider perspective. The second aim of this study was to examine possible changes of not only plasma but also urine concentrations of a broad spectrum of cytokines (16 kinds) following maximal exercise, including the time course of recovery. Although plasma TNF-alpha could not be detected throughout, it was present in urine 2 h after exercise. Plasma IL-1 beta rose significantly 2 h after exercise, but plasma IL-1 ra increased more rapidly and markedly than IL-1 beta, thus IL-1 bioactivity should be blocked at least in the circulation. Although there was only a trend toward increased plasma IL-6 concentrations after exercise, urine IL-6 rose significantly 1 h after exercise, indicating that IL-6 was released systemically but eliminated rapidly into the urine. Furthermore, it is shown for the first time that plasma and urine IL-4 concentrations were significantly elevated 2 h after exercise. Therefore, it is possible that anti-**inflammatory cytokines** might be released into the circulation as a regulatory mode of the cytokine network for adaptation against systemic inflammatory stress. Additionally, we have demonstrated that plasma concentrations of G-CSF, granulocytemacrophage CSF (GM-CSF), M-CSF, IL-8 and MCP-1 increased immediately after short-duration exercise and that the urine concentrations of these cytokines were much more pronounced than the changes observed in plasma. In conclusion, cytokines that are considered to induce systemic bioactivity following exercise are not only anti-**inflammatory cytokines** but also colony-stimulating factors and chemokines, which were secreted in an earlier phase of exercise without the kinetic involvement of traditional proinflammatory cytokines. Although the wider physiological and pathological implications are still not clearly understood, these cytokine kinetics may partly explain suppressed cell-mediated immunity and increased allergic reactions derived from a lower type-1 to type-2 cytokine ratio, along with mobilization and functional augmentation of neutrophils and monocytes. The sources and stimuli of cytokine **production** are not fully elucidated at

present, but several hypotheses based on recent experimental evidence are discussed in this **review** herein.

L27 ANSWER 4 OF 9 MEDLINE on STN
AN 2002409167 MEDLINE
DN PubMed ID: 12163213
TI Cachexia in rheumatoid arthritis.
AU Walsmith Joseph; Roubenoff Ronenn
CS Nutrition, Exercise Physiology, and Sarcopenia Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111, USA.
NC T32 AG00209-09 (NIA)
SO International journal of cardiology, (2002 Sep) 85 (1) 89-99. Journal code: 8200291. ISSN: 0167-5273.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020807
Last Updated on STN: 20021011
Entered Medline: 20021010
AB Rheumatoid arthritis is a debilitating, chronic, systemic, autoimmune disease of unknown etiology that causes destruction of joint cartilage and bone. It generally occurs between the fourth and sixth decades of life, and affects two to three times more women than men. It is characterized by joint stiffness, pain, and swelling, and is accompanied by a loss of body cell mass. This loss of cell mass, known as rheumatoid cachexia, predominates in skeletal muscle, but also occurs in the viscera and immune system. Thus, rheumatoid cachexia leads to muscle weakness and a loss of functional capacity, and is believed to accelerate morbidity and mortality in rheumatoid arthritis. Currently there is no established mechanism for rheumatoid cachexia, but it is accompanied by elevated resting energy expenditure, accelerated whole-body protein catabolism, and excess **production** of the **inflammatory cytokines**, **tumor necrosis** factor-alpha and **interleukin**-1beta. **Tumor necrosis** factor-alpha is probably the central mediator of muscle wasting in rheumatoid arthritis, and is known to act synergistically with **interleukin**-1beta to promote cachexia. In general, **tumor necrosis** factor-alpha and **interleukin**-1beta are thought to alter the balance between protein degradation and protein synthesis in rheumatoid arthritis to cause muscle wasting. The precise mechanism by which they do this is not known. Reduced peripheral insulin action and low habitual physical activity are important consequences of rheumatoid arthritis, and have also been implicated as mediators of rheumatoid cachexia. Insulin **inhibits** muscle protein degradation. Consequently, reduced peripheral insulin action in rheumatoid arthritis is thought to be permissive to cytokine-driven muscle loss. The cause of reduced peripheral insulin action in rheumatoid arthritis is not known, but **tumor necrosis** factor-alpha has been shown to interfere with insulin receptor signaling and is probably an important contributor. Low habitual physical activity has consistently been observed in rheumatoid arthritis and is an important consequence of, and contributor to, muscle wasting. In addition, low physical activity predisposes to fat gain and is believed to precipitate a negative reinforcing cycle of muscle loss, reduced physical function, and fat gain in rheumatoid arthritis, which leads to

'cachectic obesity'. To date, there is no standard treatment for rheumatoid cachexia. However, physical exercise is currently believed to be the most important and clinically relevant countermeasure against rheumatoid cachexia. In general, a combination of skeletal muscle strength training and aerobic exercise is recommended, but must be prescribed with the patient's disease status, overall health, and safety in mind. Future studies should investigate the safety, efficacy, and required dose of anti-cytokine therapy for the treatment of rheumatoid cachexia. In this **review**, we outline the current definition of rheumatoid cachexia, and discuss the etiology, pathogenesis, and treatment of rheumatoid cachexia.

L27 ANSWER 5 OF 9 MEDLINE on STN
AN 1998424150 MEDLINE
DN PubMed ID: 9753228
TI Ulcer recurrence: cytokines and inflammatory response-dependent process.
AU Arakawa T; Watanabe T; Fukuda T; Higuchi K; Fujiwara Y; Kobayashi K; Tarnawski A
CS Third Department of Internal Medicine, Osaka City University Medical School, Osaka, Japan.
SO Digestive diseases and sciences, (1998 Sep) 43 (9 Suppl) 61S-66S. Ref: 31 Journal code: 7902782. ISSN: 0163-2116.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199810
ED Entered STN: 19981008
Last Updated on STN: 19981008
Entered Medline: 19981001
AB H. pylori and nonsteroidal antiinflammatory drugs (NSAIDs) are important factors in the recurrence of peptic ulcer diseases. However, H. pylori-negative recurring ulcers can also be found in nonusers of NSAIDs. The aim of this paper is to **review** recent data pertaining to mechanisms of ulcer recurrence. Prostaglandin E2 generation is impaired in the tissues of the ulcer scar site and prostaglandin depletion induced by administration of indomethacin during the healing of experimental gastric ulcer predisposes to future ulcer recurrence. Therefore, the prostaglandin deficiency may impair the quality of ulcer healing and thus increase the likelihood of future ulcer recurrence. Persistent infiltration of polymorphonuclear cells is the most prominent finding in the gastric ulcer scar in rats treated with indomethacin. Concomitant administration of prostaglandin E1-analog with indomethacin attenuates inflammatory infiltration and reduces future ulcer recurrence. Therefore, the inflammatory responses at the ulcer scar site may be a key to the quality of ulcer healing. Recent clinical findings suggest a close relationship between the quality of ulcer healing, infiltration of neutrophils and mononuclear cells, and future ulcer recurrence. Gastroprotective drugs such as prostaglandin analogs and prostaglandin inducers improve the quality of ulcer healing and reduce future recurrence. **Production** of **inflammatory cytokines** is stimulated by ulcerogenic factors such as NSAIDs, stress, and H. pylori infection. **Inflammatory cytokines** such as **interleukin**-1beta and **tumor necrosis** factor-alpha cause recurrence of healed ulcer. Synthetic prostaglandin E2

inhibits recurrence as well as the **production** of the cytokines.

L27 ANSWER 6 OF 9 MEDLINE on STN
AN 97270788 MEDLINE
DN PubMed ID: 9125802
TI **Inhibiting inflammatory cytokines.**
AU Kluth D C; Rees A J
CS Department of Medicine and Therapeutics, University of Aberdeen, Foresterhill, Scotland.
SO Seminars in nephrology, (1996 Nov) 16 (6) 576-82. Ref: 60
Journal code: 8110298. ISSN: 0270-9295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970602
Last Updated on STN: 19970602
Entered Medline: 19970520
AB Acute glomerulonephritis is a common cause of renal dysfunction and ultimately renal failure. The inflammation involved is a tightly regulated response with pro- and anti-**inflammatory cytokines** playing key roles. **Interleukin**-1 (IL-1) and **tumor necrosis** factor (TNF) are the principal pro-**inflammatory cytokines** produced by intrinsic cells and infiltrating leukocytes. IL-1 and TNF can be directly antagonized using IL-1 receptor antagonist (IL-1ra) or binding proteins such as soluble receptors or antibodies. Alternatively, cytokines with anti-inflammatory properties can be used to decrease IL-1 and TNF synthesis, increase the **production** of their natural antagonists and deactivate inflammatory cells such as macrophages. This **review** will focus on these anti-**inflammatory cytokines**, principally IL-4, IL-6, IL-10 and IL-13, and highlight recent research of their activities in existing models of renal disease. The results of these experiments offer a promising new avenue of treatment.

L27 ANSWER 7 OF 9 MEDLINE on STN
AN 96239210 MEDLINE
DN PubMed ID: 8648424
TI Modulation of inflammation and cytokine **production** by dietary (n-3) fatty acids.
AU Blok W L; Katan M B; van der Meer J W
CS Department of General Internal Medicine, University Hospital Nijmegen, Nijmegen, The Netherlands.
SO Journal of nutrition, (1996 Jun) 126 (6) 1515-33. Ref: 131
Journal code: 0404243. ISSN: 0022-3166.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199607
ED Entered STN: 19960805
Last Updated on STN: 19960805

Entered Medline: 19960725

AB The **production** of pro-**inflammatory cytokines**, such as **interleukin**-1 and **tumor necrosis** factor, is pivotal in the response to infection. However, overproduction of these cytokines might be detrimental. It has been suggested that (n-3) fatty acids suppress inflammation and ameliorate the course of infection by decreasing the **production** of pro-**inflammatory cytokines**. We here, **review** these effects. Use of (n-3) fatty acids induced moderate clinical improvements in rheumatoid arthritis, psoriasis and colitis, but not in systemic lupus erythematosus. Data on critically ill burn or postoperative cancer patients are still inconclusive. The (n-3) fatty acids markedly **inhibited** sterile inflammation in animal studies and improved survival in some experimental infections. T cell responses decreased in healthy volunteers but remained unchanged or increased in certain patient groups. The **production** of pro-**inflammatory cytokines** decreased in most human studies. The (n-3) fatty acids increased cytokine **production** capacity in mice. Differences in cytokine-producing cell types studied may account for these paradoxical responses in humans and mice. Although the increased cytokine **production** in mice is partly mediated by effects on prostaglandins, mechanisms of action in other species remain to be elucidated. The (n-3) fatty acids may be of moderate benefit in some chronic inflammatory diseases. Their therapeutic value and possible hazards in critically ill patients remain to be established.

L27 ANSWER 8 OF 9 MEDLINE on STN
AN 92199024 MEDLINE
DN PubMed ID: 1550874
TI Relationship of TNF to interleukins.
AU Neta R; Sayers T J; Oppenheim J J
CS Armed Forces Radiobiology Research Institute, Bethesda, Maryland.
NC NO1-CO-74102 (NCI)
SO Immunology series, (1992) 56 499-566. Ref: 364
Journal code: 0404721. ISSN: 0092-6019.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199204
ED Entered STN: 19920509
Last Updated on STN: 19920509
Entered Medline: 19920428

AB It is evident from this **review** that TNF exhibits complex interactions with other cytokines at the level of **production** and in its effects. Studies designed to determine the role of TNF in the animal models or cell culture system using pure recombinant molecules have revealed that TNF never operates by itself, but instead operates within a network of cytokines. First, the multitude of exogenous as well as endogenous signals, which induce TNF **production**, concomitantly also stimulate the **production** of a battery of other **inflammatory cytokines**: IL-1, IL-6, IL-8, multiple CSFs, IFN, and TGF-beta. Moreover, TNF itself stimulates the **production** of most of these cytokines. Thus even when pure recombinant TNF is used, it readily generates the **production** of other interactive cytokines. This apparent redundancy in the **production** of cytokines with overlapping effects presumably has protective advantage for

the host. Furthermore, interaction of these cytokines is more economical and amplifies the responses to subtoxic doses of potentially harmful cytokines. Cytokine interaction may lead to either synergistic (as for many TNF-IL-1 interactions) or antagonistic effects (TNF and TGF-beta, for example). These may depend on (1) the modulation of receptor expression of one cytokine by another (IFN-gamma-enhancing receptor expression for TNF, and TGF-beta down-regulation of IL-1 receptors), (2) stabilization of the cytokine message by one another (induction of IL-6 by TNF or IL-1), (3) interactions at the level of signal transduction, (4) gene expression, or (5) at the posttranslational level. Thus the receptor repertoire, which is a function of the cell type and stage of development, actually determines the net effects of a particular combination of interactive cytokines. Clearly, the mechanisms of these interactions will need to be elucidated to better understand their biological function and to permit cytokines to be used clinically to the advantage of the host.

L27 ANSWER 9 OF 9 MEDLINE on STN
AN 91198491 MEDLINE
DN PubMed ID: 1826616
TI **Interleukin**-1 and **interleukin**-1 antagonism.
AU Dinarello C A
CS Department of Medicine, Tufts University School of Medicine, Boston, MA.
NC AI 15614 (NIAID)
SO Blood, (1991 Apr 15) 77 (8) 1627-52. Ref: 326
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199105
ED Entered STN: 19910607
Last Updated on STN: 19910607
Entered Medline: 19910521
AB The polypeptide cytokine **interleukin**-1 (IL-1) affects nearly every tissue and organ system. IL-1 is the prototype of the pro-**inflammatory cytokines** in that it induces the expression of a variety of genes and the synthesis of several proteins that, in turn, induce acute and chronic inflammatory changes. IL-1 is also the prototypic "alarm" cytokine in that it brings about increases in a variety of defense mechanisms, particularly immunologic and hematologic responses. Most studies on the biology of IL-1 have been performed in animals, but human subjects have recently been injected with recombinant IL-1 and the results confirm the two fundamental properties of IL-1 as being both a mediator of disease as well as of host defense. However, in either situation, over or continued **production** of IL-1 leads to debilitation of normal host functions; therefore, reduction of IL-1 synthesis or its effects becomes a target of therapy in many diseases. In this **review**, the structure, gene expression, synthesis, and secretion of IL-1 are described. In addition, the two IL-1 surface receptors, possible signal transduction mechanisms, various biologic activities, and **production** of IL-1 during disease states are discussed. Similarities and differences between IL-1, **tumor necrosis** factor, and IL-6 are presented. Although various agents for reducing the synthesis and/or for antagonizing the effects of IL-1 have been proposed, the recent cloning of a naturally occurring IL-1 receptor antagonist (IL-1ra) has opened new experimental and clinical

approaches. The ability of this IL-1ra to block the triggering of IL-1 receptors in animals without agonist effects has reduced the severity of diseases such as hemodynamic shock, lethal sepsis, inflammatory bowel disease, experimental arthritis, and the spontaneous proliferation of human leukemic cells.

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=> d 1-22 bib abs

L28 ANSWER 1 OF 22 MEDLINE on STN
AN 2005175790 MEDLINE
DN PubMed ID: 15807842
TI New therapies for rheumatoid arthritis.
AU Goldblatt F; Isenberg D A
CS Centre for Rheumatology, The Middlesex Hospital, University College London, Arthur Stanley House, 40-50 Tottenham Street, London W1T 4NJ, UK.. fgoldblatt@aol.com
SO Clinical and experimental immunology, (2005 May) 140 (2) 195-204. Ref: 100
Journal code: 0057202. ISSN: 0009-9104.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200505
ED Entered STN: 20050406
Last Updated on STN: 20050510
Entered Medline: 20050509
AB Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease, which continues to cause significant morbidity in affected persons. In the past few years, a number of new exciting therapeutic options have become available. These reflect the application of knowledge obtained from advancements in understanding of disease pathogenesis and underlying molecular mechanisms. A number of these therapies are outlined in the following **review**, including the various biological modifiers, in particular, anti-tumour necrosis factor-alpha agents and **interleukin**-1 (IL-1) receptor antagonists, which have been developed in recognition of the role of pro-**inflammatory cytokines** in RA. Also notable, is the current interest centring on the development and trials with B cell depletion therapies, specifically rituximab, in patients with RA. This demonstrates acknowledgment for a more significant role for B cells in the aetiology of RA, in contrast to the long held view that RA was a predominantly T cell mediated disease. To evaluate this therapeutic option for RA, salient features from recent rituximab trials have been collated. Finally, a selection of other therapeutic alternatives, including anti-IL-6 receptor monoclonal antibody and tacrolimus, and newer anti-rheumatic therapies presently in development are summarized.

L28 ANSWER 2 OF 22 MEDLINE on STN
AN 2005121652 MEDLINE
DN PubMed ID: 15753145
TI Anti-inflammatory effects of alpha-tocopherol.
AU Singh Uma; Jialal Ishwarlal
CS Laboratory for Atherosclerosis and Metabolic Research, University of California Davis Medical Center, 4635 Second Avenue, Res 1 Building, Room 3000, Sacramento, CA 95817, USA.
NC K24 AT00596 (NCCAM)
R01 AT 00005 (NCCAM)
SO Annals of the New York Academy of Sciences, (2004 Dec) 1031 195-203. Ref: 38
Journal code: 7506858. ISSN: 0077-8923.

10676089

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200506
ED Entered STN: 20050309
Last Updated on STN: 20050616
Entered Medline: 20050615
AB Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the western world. Its incidence has been increasing lately in the developing countries. Much evidence suggests a major role for inflammation in all phases of atherosclerosis. Cell adhesion molecules, cytokines, chemokines, and monocytes-macrophages as well as T lymphocytes play a pivotal role in atherogenesis. C-reactive protein (CRP), a downstream marker of inflammation, in addition to being a risk marker for CVD, could contribute to atherosclerosis. Dietary micronutrients with anti-inflammatory properties, specially alpha-tocopherol, may play an important role with regard to the prevention and treatment of CVD. alpha-Tocopherol has been shown to have anti-inflammatory effects both in vitro and in vivo. alpha-Tocopherol therapy, especially at high doses, has been shown to decrease release of pro-**inflammatory cytokines** (such as **interleukin**-1beta, **interleukin**-6, and **tumor necrosis** factor-alpha) and the chemokine **interleukin**-8, and to decrease adhesion of monocytes to endothelium. In addition, alpha-tocopherol has been shown to decrease CRP levels in patients with CVD and having related risk factors for CVD (such as diabetes and smoking). Furthermore, pro-**inflammatory cytokines** and plasminogen activator **inhibitor**-1 (PAI-1) levels have also been shown to be decreased with alpha-tocopherol supplementation in vivo. In this **review**, our focus will be on anti-inflammatory effects of alpha-tocopherol reported in in vivo studies.

L28 ANSWER 3 OF 22 MEDLINE on STN
AN 2005005857 MEDLINE
DN PubMed ID: 15631310
TI Therapeutic approaches in inflammatory bowel disease based on the immunopathogenesis.
AU Siegmund B; Zeitz M
CS Department of Medicine I, Charite Universitatsmedizin Berlin, Campus Benjamin Franklin, Germany.
SO Roczniki Akademii Medycznej w Bialymstoku (1995), (2004) 49 22-30. Ref: 74
Journal code: 9515551.
CY Poland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200503
ED Entered STN: 20050106
Last Updated on STN: 20050330
Entered Medline: 20050329
AB Our understanding of the etiology and pathogenesis of IBD has improved

extensively over the past years. At the center of the pathogenesis seems to be an excessive pro-inflammatory immune reaction towards normal intestinal flora. The different factors involved in this concept will form the focus of this **review**. The initial phase of antigen processing and presentation can be influenced by either modulation of the intestinal flora via antibiotics or probiotics or by direct stimulation of macrophages through GM-CSF treatment. Antigen recognition and activation of T-cells can be down-regulated by immunosuppressives such as azathioprine, CsA or methotrexate thus building the basis for current treatment in IBD. The pro-inflammatory character of the immune reaction is defined by the predominance of certain T-cell subpopulations. By targeting cytokines the disbalance of these subpopulation should be reconstituted. Here we will focus first on preliminary clinical as well as experimental data for the pro-inflammatory mediators IL-12 and IL-18 as well as for the anti-**inflammatory cytokine** IL-10.
Second, the clinical data for the TNFalpha antibody that has been proven to be efficacious in Crohn's disease and the associated risks will be discussed. Last, recent clinical and experimental data on targeting cell adhesion as well as intracellular signaling pathways will be presented.
In summary, with regard to this **review**, treatments, which intervene as early as possible in the initiation of the pathological immune reaction and simultaneously have a favorable side-effect profile, must be the focus of future research.

L28 ANSWER 4 OF 22 MEDLINE on STN
AN 2004354963 MEDLINE
DN PubMed ID: 15258091
TI Pathogenesis of malaria and clinically similar conditions.
AU Clark Ian A; Alleva Lisa M; Mills Alison C; Cowden William B
CS School of Biochemistry and Molecular Biology, Australian National University, Canberra, ACT 0200, Australia.. ian.clark@anu.edu.au
SO Clinical microbiology reviews, (2004 Jul) 17 (3) 509-39, table of contents. Ref: 452
Journal code: 8807282. ISSN: 0893-8512.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200409
ED Entered STN: 20040720
Last Updated on STN: 20040910
Entered Medline: 20040909
AB There is now wide acceptance of the concept that the similarity between many acute infectious diseases, be they viral, bacterial, or parasitic in origin, is caused by the overproduction of **inflammatory cytokines** initiated when the organism interacts with the innate immune system. This is also true of certain noninfectious states, such as the tissue injury syndromes. This **review** discusses the historical origins of these ideas, which began with **tumor necrosis** factor (TNF) and spread from their origins in malaria research to other fields. As well the more established proinflammatory mediators, such as TNF, **interleukin**-1, and lymphotoxin, the roles of nitric oxide and carbon monoxide, which are chiefly **inhibitory**, are discussed. The established and potential roles of two more recently recognized contributors, overactivity of the enzyme

poly(ADP-ribose) polymerase 1 (PARP-1) and the escape of high-mobility-group box 1 (HMGB1) protein from its normal location into the circulation, are also put in context. The pathogenesis of the disease caused by falciparum malaria is then considered in the light of what has been learned about the roles of these mediators in these other diseases, as well as in malaria itself.

L28 ANSWER 5 OF 22 MEDLINE on STN
AN 2004039438 MEDLINE
DN PubMed ID: 14739767
TI Regulation of matrix metalloproteinases by cytokines and reactive oxygen/nitrogen species in the myocardium.
AU Siwik Deborah A; Colucci Wilson S
CS Myocardial Biology Unit, Boston University School of Medicine, BU Medical Center, 650 Albany Street, Boston, MA 02118, USA.. dasiwik@bu.edu
SO Heart failure reviews, (2004 Jan) 9 (1) 43-51. Ref: 90
Journal code: 9612481. ISSN: 1382-4147.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200405
ED Entered STN: 20040124
Last Updated on STN: 20040518
Entered Medline: 20040517
AB Dysregulation of the myocardial extracellular matrix contributes to abnormal cardiac muscle function. Changes in the balance between matrix deposition and matrix degradation by matrix metalloproteinases (MMPs) can lead to cardiac fibrosis and dilation. In this **review**, we discuss the regulation of MMPs, their endogenous **inhibitors** (TIMPs) and collagen synthesis by **inflammatory cytokines** and reactive oxygen/nitrogen species (ROS/RNS). **Inflammatory cytokines**, such as **interleukin**-1beta and **tumor necrosis** factor-alpha, and ROS activate mitogen-activated protein kinases and stress-responsive protein kinases in cardiac cells. In non-cardiac tissues, **inflammatory cytokine** activation of these kinases is redox sensitive, suggesting ROS may also be involved in cytokine signaling in the heart. Subsequent activation of transcription factors including AP-1, Ets, and nuclear factor kappa-B leads to increased transcription of MMPs. ROS also directly activate MMPs post-translationally. In addition, **inflammatory cytokines** and ROS lead to decreased TIMP levels and collagen synthesis. Work in animal models suggests that **inhibition** of **inflammatory cytokine** or ROS signaling leads to less myocardial remodeling. Further study of the signaling of regulation of the cardiac extracellular matrix may lead to new approaches for the treatment of myocardial remodeling and failure.

L28 ANSWER 6 OF 22 MEDLINE on STN
AN 2004019152 MEDLINE
DN PubMed ID: 14715440
TI Novel mechanisms and approaches in the study of neurodegeneration and neuroprotection. a **review**.
AU Kostrzewa Richard M; Segura-Aguilar Juan
CS Department of Pharmacology, Quillen College of Medicine, East Tennessee

State University, Johnson City, TN 37614, USA.. kostrzew@etsu.edu
NC NS 39272 (NINDS)
SO Neurotoxicity research, (2003) 5 (6) 375-83. Ref: 93
Journal code: 100929017. ISSN: 1029-8428.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200402
ED Entered STN: 20040113
Last Updated on STN: 20040203
Entered Medline: 20040202
AB Cellular mechanisms involved in neurodegeneration and neuroprotection are continuing to be explored, and this paper focuses on some novel discoveries that give further insight into these processes. Oligodendrocytes and activated astroglia are likely generators of the pro-**inflammatory cytokines**, such as the **tumor necrosis** factor family and **interleukin** family, and these glial support cells express adhesion receptors (e.g., VCAM) and release intercellular adhesion molecules (ICAM) that have a major role in neuronal apoptosis. Even brief exposure to some substances, in ontogeny and sometimes in adulthood, can have lasting effects on behaviors because of their prominent toxicity (e.g., NMDA receptor antagonists) or because they sensitize receptors (e.g., dopamine D2 agonists), possibly permanently, and thereby alter behavior for the lifespan. Cell cycle genes which may be derived from microglia, are the most-recent entry into the neuroprotection schema. Neuroprotection afforded by some common substances (e.g., melatonin) and uncommon substances [e.g., nicotine, green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG), trolox], ordinarily thought to be simple radical scavengers, now are thought to invoke previously unsuspected cellular mechanisms in the process of neuroprotection. Although Alzheimer's disease (AD) has features of a continuous spectrum of neural and functional decline, in vivo PET imaging and and functional magnetic resonance imaging, indicate that AD can be staged into an early phase treatable by **inhibitors** of beta and gamma secretase; and a late phase which may be more amenable to treatment by drugs that prevent or reverse tau phosphorylation. Neural transplantation, thought to be the last hope for neurally injured patients (e.g., Parkinsonians), may be displaced by non-neural tissue transplants (e.g., human umbilical cord blood; Sertoli cells) which seem to provide similar neurotrophic support and improved behavior - without posing the major ethical dilemma of removing tissue from aborted fetuses. The objective of this paper is to invite added research into the newly discovered (or postulated) novel mechanisms; and to stimulate discovery of additional mechanisms attending neurodegeneration and neuroprotection.

L28 ANSWER 7 OF 22 MEDLINE on STN
AN 2003295744 MEDLINE
DN PubMed ID: 12823145
TI **Review** article: the expanding role of biological agents in the treatment of inflammatory bowel disease - focus on selective adhesion molecule **inhibition**.
AU Rutgeerts P; Van Deventer S; Schreiber S
CS Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium.. paul.rutgeerts@med.kuleuven.ac.be

SO Alimentary pharmacology & therapeutics, (2003 Jun 15) 17 (12) 1435-50.
Ref: 149
Journal code: 8707234. ISSN: 0269-2813.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200309
ED Entered STN: 20030626
Last Updated on STN: 20030917
Entered Medline: 20030916

AB Inflammatory bowel disease presents in various forms. Its increasing incidence indicates that modern lifestyle triggers disease in genetically susceptible individuals. We present a model for inflammatory bowel disease pathophysiology and **review** the new biological therapies available. These biological agents have been developed to antagonise the processes of pathogenic inflammation, such as the reduction in T-lymphocyte apoptosis, increase in T-lymphocyte proliferation and increase in T-lymphocyte trafficking into the intestinal mucosa. **Inhibitors** of various **inflammatory cytokines**, including some antagonists to tumour necrosis factor, are effective therapies for inflammatory bowel disease. However, this class is associated with the risk of rare, but serious, side-effects, such as opportunistic infections and demyelinating diseases. The administration of anti-**inflammatory cytokines**, including **interleukin**-10 and **interleukin**-11, may theoretically be effective in reducing inflammation, although the clinical development of some of these therapies has been terminated. The selective **inhibition** of the adhesion molecules involved in T-lymphocyte trafficking can be effective in reducing gut inflammation. Of the selective adhesion molecule **inhibitors** under investigation, natalizumab has demonstrated efficacy in inflammatory bowel disease. The future of biological therapy for inflammatory bowel disease shows promise.

L28 ANSWER 8 OF 22 MEDLINE on STN
AN 2003247391 MEDLINE
DN PubMed ID: 12769749
TI Anti-cytokines and cytokines in the treatment of rheumatoid arthritis.
AU Taylor Peter C
CS The Kennedy Institute of Rheumatology Division, Faculty of Medicine, Imperial College London, 1 Aspenlea Road, London, W6 8LH..
peter.c.taylor@ic.ac.uk
SO Current pharmaceutical design, (2003) 9 (14) 1095-106. Ref: 119
Journal code: 9602487. ISSN: 1381-6128.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20030529
Last Updated on STN: 20030628
Entered Medline: 20030627

AB The treatment approach to rheumatoid arthritis has undergone a major

evolutionary change in recent years in part as a consequence of growing appreciation of the severity of this condition and in part due to very considerable progress in understanding the important role of cytokines in the immunopathogenesis of this disease. The major focus of this **review** is on the rationale for targeting TNFalpha and IL-1 in rheumatoid arthritis and the results of clinical studies designed to assess the validity of this therapeutic approach. Recently published studies confirm that the long term use of a several biological agents targeting TNFalpha give rise to sustained improvements in symptoms and signs of rheumatoid disease and, furthermore, that TNFalpha blockade protects joints from structural damage. Although these drugs are well tolerated and have a good overall safety profile, pitfalls to the use of anti-TNFalpha agents apparent with increasing clinical experience include rare cases of tuberculosis. The mechanism of action of anti-TNFalpha therapy is discussed. Clinical trials of **interleukin**-1 receptor antagonist show relatively modest anti-inflammatory efficacy and an effect on X-ray indicative of retardation of joint damage. Other pro-**inflammatory cytokines** representing potential therapeutic targets include interferon-beta, interferon-alpha, IL-6, IL-15, IL-17 and IL-18. I will consider preliminary data, where available, arising from clinical trials designed to **inhibit** the activity of such molecules. In this **review** I will also discuss the rationale and preliminary data for other potential therapeutic strategies designed to augment the activity of anti-**inflammatory cytokines** such as IL-4, IL-10, and IL-11 in rheumatoid disease.

L28 ANSWER 9 OF 22 MEDLINE on STN
AN 2003097576 MEDLINE
DN PubMed ID: 12609522
TI Cytokines and the immune-testicular axis.
AU Hedger Mark P; Meinhardt Andreas
CS Monash Institute of Reproduction and Development, Monash University, 27-31 Wright Street, Clayton, Melbourne, Victoria 3168, Australia.. mark.hedger@med.monash.edu.au
SO Journal of reproductive immunology, (2003 Feb) 58 (1) 1-26. Ref: 154
Journal code: 8001906. ISSN: 0165-0378.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200310
ED Entered STN: 20030302
Last Updated on STN: 20031031
Entered Medline: 20031030
AB Cytokines are regulatory proteins involved in haematopoiesis, immune cell development, inflammation and immune responses. Several cytokines have direct effects on testicular cell functions, and a number of these are produced within the testis even in the absence of inflammation or immune activation events. There is compelling evidence that cytokines, in fact, play an important regulatory role in the development and normal function of the testis. Pro-**inflammatory cytokines** including **interleukin**-1 and **interleukin**-6 have direct effects on spermatogenic cell differentiation and testicular steroidogenesis. Stem cell factor and leukaemia **inhibitory** factor, cytokines normally involved in haematopoiesis, also play a role in spermatogenesis. Anti-**inflammatory cytokines** of the transforming growth

factor-beta family are implicated in testicular development. Consequently, local or systemic up-regulation of cytokine expression during injury, illness or infection may contribute to the disruption of testicular function and fertility that frequently accompanies these conditions. The aim of this **review** is to provide a very brief summary of the extensive literature dealing with cytokines in testicular biology, and to follow this with some speculation concerning the significance of these molecules in interactions between the immune system and the testis.

L28 ANSWER 10 OF 22 MEDLINE on STN
AN 2003081731 MEDLINE
DN PubMed ID: 12593604
TI Perspective of cytokine regulation for periodontal treatment: fibroblast biology.
AU Takashiba Shogo; Naruishi Koji; Murayama Yoji
CS Department of Pathophysiology-Periodontal Science, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan.
SO Journal of periodontology, (2003 Jan) 74 (1) 103-10. Ref: 72
Journal code: 8000345. ISSN: 0022-3492.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Dental Journals; Priority Journals
EM 200305
ED Entered STN: 20030221
Last Updated on STN: 20030508
Entered Medline: 20030507
AB Efforts to understand the pathogenesis of periodontal diseases have been underway for decades. Studies of immunological aspects in addition to the structural components of gingival fibroblasts showed that the fibroblasts actively participate in immune and inflammatory events in periodontal diseases. Future strategies for the prevention and treatment of periodontal diseases should biologically regulate fibroblast activities. These cells are surrounded by monocyte-derived proinflammatory cytokines such as **interleukin**-1 beta (IL-1beta), **tumor necrosis** factor-alpha (TNF-alpha), and lymphocyte-derived **interleukin**-6 (IL-6) in inflamed gingival tissue. Recent anti-cytokine therapy for inflammatory diseases including rheumatoid arthritis aimed to **inhibit** the binding of cytokines to targeted cells such as fibroblasts and condrocytes. IL-1beta and TNF-alpha are thought to be therapeutic targets because these cytokines are essential for the initiation of inflammatory immune reactions and are produced for prolonged periods in inflammatory diseases. IL-6 is also a target, because it is abundantly present in inflammatory lesions and activates fibroblasts in the presence of soluble IL-6 receptor. In addition, these cytokines accelerate gingival fibroblasts to produce collagenolytic enzymes, resulting in tissue destruction. Soluble receptors for IL-1beta and TNF-alpha are suggested to be candidates for therapeutic molecules, but soluble receptor for IL-6 is suggested to be a factor-stimulating fibroblast. This paper will **review** the utilization of soluble receptors specific to **inflammatory cytokines** which potentially stimulate fibroblasts to regulate biological events involved in the pathogenesis of periodontal diseases.

L28 ANSWER 11 OF 22 MEDLINE on STN
AN 2003043752 MEDLINE
DN PubMed ID: 12553500
TI Protein C pathway in sepsis.
AU Esmon Charles T
CS Cardiovascular Biology Research Program, Oklahoma Medical Research Foundation, 825 NE 13th Street, Oklahoma City, OK 73104, USA.. Charles-Esmon@omrf.ouhsc.edu
SO Annals of medicine, (2002) 34 (7-8) 598-605. Ref: 53
Journal code: 8906388. ISSN: 0785-3890.
CY Sweden
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20030130
Last Updated on STN: 20030429
Entered Medline: 20030428
AB The goals of this chapter are to provide a brief **review** of the biology of the protein C pathway and some of the features of the pathway that make it uniquely positioned to control microvascular coagulation and control the acute inflammatory response. Activated protein C works as an antithrombotic agent by inactivating factors Va and VIIIa. It is particularly effective at preventing microvascular thrombosis. Platelets may provide a margin of safety for activated protein C as an antithrombotic. Approximately 25% of the factor V/Va in plasma is contained within the platelet and hence resistant to time dependent inactivation by activated protein C. In addition, factor Va bound to the platelet surface is relatively resistant to inactivation by activated protein C. Activated protein C also facilitates clot lysis by **inhibiting** plasminogen activator **inhibitor** 1, a process that is accelerated markedly by vitronectin. **Inflammatory cytokines** like **tumor necrosis** factor alpha (TNFalpha) and **interleukin**-1beta (IL-1beta) downregulate two key components of the protein C activation complex, thrombomodulin and the endothelial cell protein C receptor resulting in decreased protein C activation. Activated protein C in turn has been shown in several animal models and in vitro to **inhibit** TNF elaboration in response to endotoxin. This **inhibition** appears to be due to diminished nuclear factor kappaB (NF kappaB) expression and nuclear translocation. Activated protein C has been shown to reduce the rate of death due to severe sepsis. This reduction may be due to both the anticoagulant effects as demonstrated by a reduction in D-dimer and inflammatory effects as demonstrated by a reduction in **interleukin** 6.

L28 ANSWER 12 OF 22 MEDLINE on STN
AN 2002628751 MEDLINE
DN PubMed ID: 12385830
TI Testicular macrophage modulation of Leydig cell steroidogenesis.
AU Hales Dale Buchanan
CS Department of Physiology and Biophysics (M/C901), University of Illinois at Chicago, Chicago, IL 60612-7342, USA.. dbhale@uic.edu
SO Journal of reproductive immunology, (2002 Oct-Nov) 57 (1-2) 3-18.. Ref: 120
Journal code: 8001906. ISSN: 0165-0378.

CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200305
ED Entered STN: 20021019
Last Updated on STN: 20030528
Entered Medline: 20030527
AB This **review** will highlight recent advances in the study of the immuno-endocrinology of the testis, in particular how macrophage-derived inflammatory mediators affect Leydig cell functions. Both the beneficial and deleterious outcomes resulting from macrophage-Leydig cell interactions are discussed. A brief overview of testicular physiology is provided that discusses the functional and anatomical compartmentalization of the testis into the gamete and endocrine compartments where spermatogenesis and testosterone biosynthesis take place, respectively. The process of steroidogenesis including the activities of the steroidogenic enzymes and the role of steroidogenic acute regulatory protein (StAR) are described. The close physical association between Leydig cells and interstitial testicular macrophages suggests that these cells are functionally related. Under normal physiological and non-inflammatory conditions macrophages play an important role in Leydig cell development. If macrophages are absent from the testicular interstitium, Leydig cells fail to develop normally, which suggest that macrophages provide essential growth and differentiation factors for Leydig cells. In contrast, when macrophages are activated and elaborate inflammatory mediators, Leydig cell steroidogenesis is **inhibited**. Activated macrophages produce pro-**inflammatory cytokines** such as **interleukin**-1 (IL-1) and **tumor necrosis** factor (TNF) that are profoundly **inhibitory** to Leydig cells and appear to act as transcriptional repressors of steroidogenic enzyme gene expression. Macrophages also produce reactive oxygen species (ROS) such as hydrogen peroxide, which also **inhibits** Leydig cell functions. ROS appear to act acutely by perturbing Leydig cell mitochondria resulting in the **inhibition** of StAR protein expression. One important consequence of this immune modulation of Leydig cell function may be manifest behaviorally by switching the affected animal from 'testosterone' behavior, to 'sickness' behavior. Increased interest in immune-endocrine control of reproductive function over the past decade has stimulated research into the molecular and biochemical immunopathophysiology of the reproductive system. As investigations unravel mechanisms underlying reproductive dysfunction caused by inflammation and infection, an understanding of the role that immune-endocrine interactions play in the normal physiology of the reproductive system has emerged.

L28 ANSWER 13 OF 22 MEDLINE on STN
AN 2002409158 MEDLINE
DN PubMed ID: 12163222
TI Cachexia: a therapeutic approach beyond cytokine antagonism.
AU von Haehling S; Genth-Zotz S; Anker S D; Volk H D
CS Department of Clinical Cardiology, National Heart & Lung Institute, Royal Brompton Hospital, London, UK.: stephan.von.haehling@web.de
SO International journal of cardiology, (2002 Sep) 85 (1) 173-83. Ref: 92
Journal code: 8200291. ISSN: 0167-5273.
CY Ireland

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020807
Last Updated on STN: 20021011
Entered Medline: 20021010
AB Cachexia is seen in a number of chronic diseases, and it is always associated with a poor prognosis. Irrespective of etiology, the development of cachexia appears to share a common pathophysiological pathway. This includes induction of proteasome-dependent myofibril-degradation, which is thought to be secondary to stimulation by enhanced levels of pro-**inflammatory cytokines**. Elevation of **tumor necrosis** factor-alpha (TNFalpha) and other plasma cytokines has been demonstrated in many conditions associated with cachexia. Despite improved pathophysiological understanding, a specific treatment for cachexia has not yet been established. Whilst direct TNFalpha antagonism has therapeutic appeal, this **review** will focus on manipulation of downstream pathways and the potential benefits. For example, nuclear factor-kappaB (NF-kappaB) is one of the most important signal transducers of TNFalpha, and drugs targeting this signalling cascade might be useful in the treatment of cachexia. Although the use of some of these substances, for example glucocorticoids, remains controversial, others may prove beneficial in the treatment of this syndrome. The role of other approaches such as proteasome-**inhibitors** remains to be elucidated. Alternatively, **interleukin**-10 and other immunosuppressive cytokines may also be able to counterbalance certain features of cachexia.

L28 ANSWER 14 OF 22 MEDLINE on STN
AN 2002409157 MEDLINE
DN PubMed ID: 12163221
TI Cytokines, apoptosis and cachexia: the potential for TNF antagonism.
AU Sharma Rakesh; Anker Stefan D
CS Department of Clinical Cardiology, National Heart and Lung Institute, Imperial College School of Medicine, London, UK.
SO International journal of cardiology, (2002 Sep) 85 (1) 161-71. Ref: 78
Journal code: 8200291. ISSN: 0167-5273.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020807
Last Updated on STN: 20021011
Entered Medline: 20021010
AB The cachexia syndrome is characterised by progressive weight loss and depletion of lean body mass and has long been recognised as a poor prognostic sign. Whilst the clinical features of the wasting process are readily apparent, its pathogenesis is complex and poorly understood. There is increasing evidence that the immune system, in particular **inflammatory cytokines**, may play an important role in

the development of cachexia. The cytokine considered to be the most relevant to this process is **tumor necrosis** factor alpha (TNF), although other mediators such as **interleukin** (IL) 1, IL-6 and interferon gamma have also been implicated. Apoptosis represents a potential pathway by which wasting can occur in chronic diseases. Cytokines and their corresponding receptors are known to be important regulators of cell death. Apoptosis has been demonstrated in the skeletal muscle of patients with chronic heart failure (CHF) and is thought to be partly responsible for the significant impairment of functional work capacity associated with this condition. An understanding of the mechanisms that regulate muscle protein breakdown is essential for the development of strategies for treating or even preventing muscle cachexia in patients. It is the aim of this article to **review** the role of **inflammatory cytokines**, particularly TNF, in the pathogenesis of wasting and also the potential for anti-cytokine therapy. Although this **review** will concentrate predominantly on the syndrome of CHF, other chronic illnesses such as liver disease, cancer, and sepsis will also be discussed.

L28 ANSWER 15 OF 22 MEDLINE on STN
AN 2002168043 MEDLINE
DN PubMed ID: 11899850
TI [Cytokines in rheumatoid arthritis. I. Proinflammatory cytokines]. Cytokiny w reumatoidalnym zapaleniu stawow. I. Cytokiny prozapalne.
AU Klimiuk P A; Sierakowski S
CS Klinika Reumatologii i Chorob Wewnetrznych Akademii Medycznej w Bialymstoku.. klimp@amb.edu.pl
SO Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego, (2001 Dec) 11 (66) 510-3. Ref: 49
Journal code: 9705469. ISSN: 1426-9686.
CY Poland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Polish
FS Priority Journals
EM 200204
ED Entered STN: 20020320
Last Updated on STN: 20020426
Entered Medline: 20020425
AB Proinflammatory cytokines play an important role in the pathogenesis of rheumatoid arthritis. It is why they became the targets for new therapies. In this **review** we describe their expression in synovial tissue, synovial fluid and in serum, and correlation with disease activity. Particular attention was paid to the possibilities of the alternative treatment strategies modifying the balance of cytokine network, in the rheumatoid arthritis patients, towards limiting their proinflammatory activity. **Inhibiting** the action of proinflammatory cytokines by using their specific **inhibitors** or anti-**inflammatory cytokines** have shown significant clinical benefits with mild side effects.

L28 ANSWER 16 OF 22 MEDLINE on STN
AN 2002141328 MEDLINE
DN PubMed ID: 11849114
TI Cytokine **inhibitors** in the treatment of rheumatoid arthritis.
AU Gabay Cem

10676089

CS Division of Rheumatology, University Hospital of Geneva, 26 Avenue Beau-Sejour, 1211 Geneva 14, Switzerland.. Cem.Gabay@hcuge.ch
SO Expert opinion on biological therapy, (2002 Feb) 2 (2) 135-49. Ref: 126
Journal code: 101125414. ISSN: 1471-2598.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20020307
Last Updated on STN: 20030128
Entered Medline: 20030127
AB Rheumatoid arthritis (RA) is an immune-mediated disease characterised by articular inflammation and subsequent tissue damage leading to severe disability and increased mortality. A variety of cytokines are produced locally in the rheumatoid joints. Numerous studies have demonstrated that IL-1 and TNF-alpha, two prototypic pro-**inflammatory cytokines**, play an important role in the mechanisms involved in synovial inflammation and in progressive joint destruction. Indeed, the administration of TNF-alpha and IL-1 **inhibitors** in patients with RA led to a dramatic improvement of clinical and biological signs of inflammation and a reduction of radiological signs of bone erosion and cartilage destruction. However, despite these encouraging results, a significant percentage of patients do not respond to these agents, suggesting that other mediators are also involved in the pathophysiology of arthritis. This **review** describes the results of clinical trials with TNF-alpha **inhibitors** and a specific IL-1 **inhibitor** (IL-1 receptor antagonist [IL-1Ra]). In addition, other therapeutic strategies are also discussed.

L28 ANSWER 17 OF 22 MEDLINE on STN
AN 2000231607 MEDLINE
DN PubMed ID: 10767254
TI Anti-**inflammatory cytokines**.
CM Comment in: Chest. 2000 Apr;117(4):932-4. PubMed ID: 10767220
AU Opal S M; DePalo V A
CS Infectious Disease Division, Brown University School of Medicine, Providence, RI, USA.. Steven_Opal@brown.edu
SO Chest, (2000 Apr) 117 (4) 1162-72. Ref: 109
Journal code: 0231335. ISSN: 0012-3692.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200005
ED Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511
AB The anti-**inflammatory cytokines** are a series of immunoregulatory molecules that control the proinflammatory cytokine response. Cytokines act in concert with specific cytokine **inhibitors** and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in systemic inflammatory states are increasingly recognized. Major

anti-**inflammatory cytokines** include **interleukin** (IL)-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13. Specific cytokine receptors for IL-1, **tumor necrosis** factor-alpha, and IL-18 also function as proinflammatory cytokine **inhibitors**. The nature of anti-**inflammatory cytokines** and soluble cytokine receptors is the focus of this **review**. The current and future therapeutic uses of these anti-**inflammatory cytokines** are also **reviewed**.

L28 ANSWER 18 OF 22 MEDLINE on STN
AN 1999448608 MEDLINE
DN PubMed ID: 10519163
TI Cytokines in heart failure: pathogenetic mechanisms and potential treatment.
AU Dibbs Z; Kurrelmeyer K; Kalra D; Seta Y; Wang F; Bozkurt B; Baumgarten G; Sivasubramanian N; Mann D L
CS Department of Medicine, Veterans Administration Medical Center, Houston, TX 77030, USA.
NC P50 HL-O6H (NHLBI)
SO Proceedings of the Association of American Physicians, (1999 Sep-Oct) 111 (5) 423-8. Ref: 54
Journal code: 9514310. ISSN: 1081-650X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124
AB Recent studies have shown that patients with heart failure overexpress a class of biologically active molecules, generically referred to as pro-**inflammatory cytokines**. This article will **review** recent clinical and experimental material that suggests that pro-**inflammatory cytokines** such as **tumor necrosis** factor-alpha (TNF-alpha), **interleukin**-1 (IL-1), and **interleukin**-6 (IL-6) may play a role in the pathogenesis of congestive heart failure. In addition, we will **review** recent studies that suggest that antagonizing cytokines may represent a novel target for heart failure therapy.

L28 ANSWER 19 OF 22 MEDLINE on STN
AN 1999055078 MEDLINE
DN PubMed ID: 9817746
TI Airway smooth muscle as a target of glucocorticoid action in the treatment of asthma.
AU Hirst S J; Lee T H
CS Department of Allergy and Respiratory Medicine, UMDS, Thomas Guy House, Guy's Hospital, London, United Kingdom.. s.hirst@umds.ac.uk
SO American journal of respiratory and critical care medicine, (1998 Nov) 158 (5 Pt 3) S201-6. Ref: 63
Journal code: 9421642. ISSN: 1073-449X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981221
AB Glucocorticoids are highly effective in the control of asthma and suppression of airway inflammation. The cellular and molecular mechanisms involved in the anti-inflammatory actions of glucocorticoids are becoming clearer. Although it is apparent that glucocorticoids have effects on many aspects of inflammation, it is not certain which actions on which cell types are the most critical in controlling asthma. Airway smooth muscle cells represent a significant proportion of all cells present in the airways and might therefore be expected to be a prominent cellular target for inhaled steroids. Despite this, little is known of the action of glucocorticoids on airway smooth muscle. It is becoming clear that in addition to its contractile properties, airway smooth muscle can potentially contribute to the pathogenesis of asthma by increased proliferation and by expression and secretion of pro-**inflammatory cytokines** and mediators, which in turn may lead to the activation and recruitment of key inflammatory cells in the airways. This **review** examines the action of glucocorticoids on some of the diverse functions of airway smooth muscle that are implicated in remodeling of the airways in asthma. Glucocorticoids either directly or indirectly modulate contraction of airway smooth muscle by suppressing agonist-induced increases in intracellular calcium levels or by downregulating or uncoupling receptors linked to contraction (e.g., muscarinic M2 or M3, histamine H1 receptors). In addition, glucocorticoids may augment relaxation of airway smooth muscle by increasing activation of either cyclic AMP-dependent (e.g., increased expression of beta2-adrenoceptors, reduced homologous desensitization of beta2-adrenoceptors) or AMP-independent mechanisms (e.g., increased Na+/K+ electrogenic pump activity). In addition to their effects on contraction, glucocorticoids are also effective antiproliferative agents in airway smooth muscle, but under some circumstances may also contribute to proliferation by **inhibiting** the antiproliferative effect of high concentrations of **tumor necrosis** factor alpha in these cells. Glucocorticoids also suppress induction of cyclooxygenase-2 in human airway smooth muscle cells and the subsequent synthesis and release of arachidonic acid metabolites, particularly prostaglandin E2. The potential of airway smooth muscle to recruit and activate pro-inflammatory cells such as the eosinophil may also be reduced by glucocorticoids, as they are effective in preventing the release of several cytokines (e.g., RANTES, **interleukin**-8, and granulocyte macrophage colony-stimulating factor). The possibility exists that as we begin to understand and speculate more about the likely role of airway smooth muscle in the pathogenesis of asthma, it may be necessary to reconsider airway smooth muscle as an important cellular target for the action of glucocorticoids in the treatment of asthma.

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TI The role of cytokines in the pathogenesis of acute pancreatitis.
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AB BACKGROUND: The systemic manifestations of acute pancreatitis are responsible for the majority of pancreatitis-associated morbidity and mortality and are now believed to be due to the actions of specific **inflammatory cytokines**. This report summarizes what is known about the role of cytokines in the pathogenesis of acute pancreatitis. METHODS: Comprehensive literature **review** of experimental pancreatitis as well as all reports of cytokine involvement during clinical pancreatitis. RESULTS: Several cytokines and other noncytokine inflammatory mediators are produced rapidly during pancreatitis. These mediators arise in many tissues in a predictable fashion independent of the animal model used or the underlying etiology in human disease. Preventing the activities of these mediators has a profound beneficial effect in experimental animals. CONCLUSIONS: A few recently described inflammatory mediators are believed to be primarily responsible for the systemic manifestations of acute pancreatitis and its associated distant organ dysfunction. The predictable nature in which they are produced may allow for novel approaches to treating this disease. Am J Surg.